Remarks

Claims 1-66 and 81-83 are pending in this application. Claims 11 and 12 have been amended. Claims 81-83 have been added. Claims 1, 66, and 81-83 are the only independent claims pending.

The amendments and newly added claims do not include new matter.

Claims 11 and 12 have been amended to delete the word "concentrated" used to describe various strong acids and bases. This amendment is made simply to resolve the Examiner's concern regarding the metes and bounds of "concentrated," and does not surrender any of the subject matter originally claimed.

Claim 81 is essentially claim 1, rewritten to highlight that the effect of performing the steps recited in both claims is inducement of a type 1 inflammatory response (i.e., the cause of the tumor cell death recited in claim 1). The fact that the recited method is used to induce a type 1 inflammatory response is disclosed throughout the specification, for example at page 6, lines 8-13.

Claim 82 is essentially claim 1, amended to highlight the fact that the two type 1 inflammatory response-(IR1-)promoting agents must be administered in an amount effective to induce a type 1 inflammatory response. This language is supported implicitly throughout the specification, and more specifically for example at page 18, line 13, through page 19, line 3.

Claim 83 is essentially claim 1, rewritten to highlight that the recited agents are "co-administered." The Applicant notes that co-administration is specifically defined in the specification at the paragraph bridging pages 8 and 9. Co-administration of the agents recite in newly-added claim 69 is supported in the specification, for example at page 12, lines 4-6.

Statement of the Substance of the 29 July 2003 Interview

This statement is required by 37 C.F.R. § 1.133(b).

A telephonic interview was conducted on 29 July 2003 among Examiner Misook Yu, Examiner Anthony Caputa, Applicant Eugene Roussel, and Applicant's representative Gary D. Colby. A Draft Response and Request for Consideration (not for entry) had previously been transmitted to the Examiners.

Rejections of claims 2 and 4-6 were not discussed during the interview.

During the course of the interview, the obviousness rejection in the 11 April 2003 Office Action was discussed. The Applicant asserted that the cited references do not disclose all elements of the claimed methods, that there was no motivation to combine the cited references, and no expectation that the methods disclosed in the cited references could be used synergistically, or even compatibly. The Applicant highlighted the fact that the prior art does not teach or suggest local induction of a type 1 inflammatory response in a tumor. Agreement was not reached with the Examiners, and the rejection was not withdrawn. The Applicant was invited to submit detailed written arguments in support of his position, which will be carefully considered by the Examiner on receipt.

The rejection of claims 11 and 12 with regard to the use of the word "concentrated" was briefly discussed in the interview. The Examiners agreed that extrinsic evidence, if submitted, might suffice to show a sufficiently definite meaning of the term to justify its inclusion in the claims.

Each of the Examiner's objections or rejections is addressed below in the order they were presented in Paper No. 22.

Rejection Pursuant to 35 U.S.C. § 112, First Paragraph

Claims 2 and 4-6 stand rejected pursuant to 35 U.S.C. § 112, first paragraph. In the Examiner's view, the claimed methods involve use of proteases to

induce death of tumor cells. The Examiner asserts that proteases would not be expected to kill tumor cells.

The Applicant respectfully contends that the Examiner misunderstands the role of one or more proteases in the claimed methods. As recited in the rejected claims, proteases are but one example of "antigen-releasing agents" disclosed in the specification. As indicated in the specification at page 10, lines 9-17, the role of an antigen-releasing agent in the claimed methods is simply to induce release of protein fragments or other antigens from the surface of tumor cells. The specification discloses (e.g., at page 12, lines 25 and 26) that antigen-releasing agents can, but need not, also kill tumor cells. Induction of tumor cell antigen release is thought to contribute to leukocyte recruitment and activation and enhancing the type 1 inflammatory response that is induced by performing the entire method that is recited in the claims.

Examining the rejected claims as a whole, the Examiner will understand that it is immaterial whether a protease will induce tumor cell death, so long as the other portions of the claimed method are performed. For these reasons, the Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 2 and 4-6 pursuant to 35 U.S.C. § 112, first paragraph.

Rejection Pursuant to 35 U.S.C. § 112, Second Paragraph

Claims 2, 11, and 12 stand rejected pursuant to 35 U.S.C. § 112, second paragraph.

The Examiner questions the meaning of the term "tumor de-bulking agent" in claim 2, and suggests that a proper interpretation of this term is as a synonym of protease. The Applicant respectfully contends that this interpretation is not accurate. A better appreciation of the term can be obtained by reviewing the paragraph that bridges pages 12 and 13 of the specification. Simply put, a "tumor de-bulking agent" is any antigen-releasing agent that exhibits significant tumor cell cytotoxicity. For example, simple proteases can clip antigens from cells, but will not necessarily kill any tumor cells.

By contrast, other antigen-releasing agents, such as strong acids (e.g., a small volume of 10 M HCl locally injected into a tumor mass) will induce release of antigens from tumor cells and will also kill tumor cells which it contacts. Thus, concentrated HCl is both an antigen-releasing agent and a tumor-debulking agent. The Applicant respectfully contends that a skilled artisan is aware of a wide variety of antigen-releasing agents that are available in the art, and is also aware of which of those antigen-releasing agents would also be considered tumor de-bulking agents. The Applicant requests that the Examiner reconsider and withdraw the rejection of claim 2 pursuant to 35 U.S.C. § 112, second paragraph.

The Examiner objects to the terms "concentrated hydrochloric acid" and "concentrated sulfuric acid' in claim 11 and the terms "concentrated sodium hydroxide" and "concentrated potassium hydroxide" in claim 12. The Examiner suggests that it is necessary to define how concentrated is "concentrated." The Applicant has instead deleted the term "concentrated." For this reason, the Applicant believes that the Examiner's rejection of claims 11 and 12 pursuant to 35 U.S.C. § 112, second paragraph, is moot and should be withdrawn.

Discussion of the Lee, Tannenbaum, and Lanni References

The Examiner makes numerous obviousness-type rejections, all of which are based on the Lee et al. reference (Lee et al., 2000, J. Immunol. 164:231-239) in combination with either Tannenbaum et al. (1998, J. Immunol. 161:927-932) or Lanni (1997, Proc. Natl. Acad. Sci. USA 94:9679-9683). Owing to the centrality of these references to the Examiner's obviousness-type rejections, the Applicant first discusses what these three references teach. The relevance of the shortcomings in the teachings of the references is thereafter discussed separately in connection with the particular claim rejections.

Discussion of the Lee Reference

Lee investigated Fas-mediated apoptosis of tumor cells. Fas is a cell-surface protein that is expressed on a wide variety of cell types, including at least several solid tumor cell types and many non-tumorous immune cell types. By mechanisms that are not relevant here, cells that express Fas undergo apoptosis when FasL protein binds with Fas protein on their surface. At least certain antibodies that bind specifically with Fas protein can also cause Fas-expressing cells to undergo apoptosis. Lee used such an antibody in his experiments, and designated the antibody "anti-Fas antibody."

Lee examined the ability of anti-Fas antibody to cause Renca cells to undergo apoptosis. Lee observed that expression of Fas protein was low on Renca cells when the cells were maintained *in vitro* in medium that does not contain IFN-g or TNF (see enclosed composition of RPMI 1640 defined medium, obtained from Euroclone Ltd. UK web site). Addition of IFN-g, TNF, or both to the defined medium enhanced expression of Fas on Renca cells (see Figure 1A). Expression of Fas on Renca cells could also be enhanced by transfecting the cells with a commercial cloning vector into which the coding region of Fas cDNA had been inserted (i.e., to express Fas at a high level from the vector - See Figure 2A). Renca cells that were not induced to express Fas at a high level (i.e., on account of either transfection or culture in the presence of IFN-g and TNF) did not undergo apoptosis when contacted with anti-Fas antibody (see Figures 1C and 2C). Cells that were induced to express Fas at a high level underwent apoptosis when contacted with anti-Fas antibody. The conclusion to be drawn from these experiments is that Renca cells grown in defined medium do not express Fas at a sufficiently high level to render them sensitive to Fas-mediated apoptosis. A corollary of that conclusion is that expression of Fas must be induced in Renca cells grown in defined medium in order to confer sensitivity to Fas-mediated apoptosis in those cells.

Lee next injected Renca cells subcutaneously into mice as a model of *in vivo* tumor growth. When non-treated Renca cells were injected into mice, the mice

developed tumors that grew at a characteristic rate (open circles in Figure 4A; solid circles in Figure 4B). When Fas-transfected (i.e., Fas-overexpressing) Renca cells were injected into mice, the rate of tumor growth was significantly slowed (Figure 4A, squares and triangles; Figure 4B, filled triangles).

Following that observation, Lee investigated the effect of endogenous production of IFN-g on the apparent growth-slowing effect of Fas-overexpression in Renca cells. Lee injected non-treated Renca cells into normal mice and into mice that did not express endogenous IFN-g. Lee also injected Fas-transfected Renca cells into the same two types of mice. In normal mice, the rate of non-treated Renca cell tumor growth was significantly faster than the rate of Fas-transfected Renca cell tumor growth. In mice that did not express endogenous IFN-g, the rate of growth of non-treated and Fas-transfected Renca cell tumors were more nearly the same (see Figure 7A). Nonetheless, the rate of growth of the two tumor types was faster in mice that did not express endogenous IFN-g than in normal mice (i.e., compare open and solid symbols in Figures 7A). The conclusion to be drawn from these results (indeed, the conclusion Lee drew - see the paragraph bridging the columns on page 234), is that endogenous IFN-g may be necessary for the tumor-growth-slowing effect that appears to be attributable to expression of Fas protein.

It is noteworthy that Lee did not administer any cytokine to any of the mice in the studies described in the reference. An ordinarily-skilled artisan would consider use of IFN-g and TNF in the defined medium of Renca cells cultured *in vitro* to be a way to approximate the tumor cell environment *in vivo*. At no point does Lee teach or suggest that it is necessary or desirable to administer IFN-g, TNF, or any other cytokine to the tumor of an animal (either locally or systemically), nor is there any teaching or suggestion in Lee of what might happen if one did. In all of the experiments in which alleviation of tumors in mice were studied, the only agents administered to the mice were the tumor cells themselves and (in some experiments), anti-Fas antibodies.

Lee does not teach or suggest local administration of IFN-g, a second IR1-promoting agent, or a leukocyte attractant to a tumor in any animal.

Turning to the Examiner's characterization of the Lee reference, the Examiner asserts that anti-Fas antibody in combination with IFN-g and TNF "has the highest anti-tumor effect." The Examiner fails to recognize that Lee did not administer IFN-g or TNF to any animal, or even to any tumor. The only experiments described in Lee in which IFN-g and TNF were used involved cultured cells maintained in a serum-free defined medium supplemented with IFN-g and TNF. Furthermore, Lee concluded no more than that endogenous levels of IFN-g or TNF were necessary to support the Fas-mediated anti-tumor effect attributed to anti-Fas antibodies. Lee did not conclude or suggest that greater-than-endogenous levels of IFN-g and/or TNF would offer any therapeutic benefit. Neither the Examiner nor any ordinarily-skilled artisan can make that conclusion based on the information in the Lee reference.

Discussion of the Tannenbaum Reference

Tannenbaum investigated the dependence of the anti-tumor effects attributed to IL-12 on expression of the known chemoattractants Mig and IP-10. Tannenbaum injected Renca (tumor) cells into mice subcutaneously. In the absence of treatment, the Renca cells developed into tumors. When IL-12 was intraperitoneally administered to the mice, tumor regression was observed. Tumoral expression of Mig and IP-10 was detected in IL-12-treated animals. The tumor regression-inducing effect of IL-12 was inhibited or ablated if antibodies that bind specifically with either IP-10 or Mig were administered to the animals. The conclusion that an ordinarily-skilled artisan would draw from these results (and the conclusion drawn by Tannenbaum) is that endogenous expression of Mig and IP-10 is involved in the physiological mechanism (whatever that mechanism might be) of IL-12-mediated tumor regression.

Tannenbaum recognized (page 931, first partial paragraph, second full sentence) that IL-12 treatment of mice induced endogenous production of IFN-g, but does not teach or suggest that administration of non-endogenous IFN-g would be expected to yield any benefit.

In the final paragraph, Tannenbaum speculates that interactions between and among cytokines expressed in a patient's tumor can contribute to anti-tumor effects. However, the Tannenbaum does not teach or suggest at any point that administration of more than a single cytokine to a patient will enhance the anti-tumor effect of the single cytokine.

Tannenbaum discloses administration of IL-12 (a suitable IR1-promoting agent, as disclosed in the specification) to mice with tumors, but does not teach locally administering an antigen-releasing agent, IFN-g, or a leukocyte attractant to a tumor in any animal.

Turning to the Examiner's characterization of the Tannenbaum reference, the Examiner asserts that Tannenbaum discloses "that several cytokines applicant calls 'leukocyte attractant' are known in the art to have anti-tumor effects." The only cytokine leukocyte attractants disclosed in the Applicant's specification that are mentioned in Tannenbaum are IP-10 and Mig. Tannenbaum reports the results of others (page 931, right column, lines 16-18), namely that others have observed limited tumor necrosis when IP-10 and Mig are injected into tumors. Tannenbaum teaches that the anti-tumor effects of IL-12 (i.e., T cell-mediated effects) greatly overwhelm any potential anti-tumor effect that may have been attributable to endogenous Mig or IP-10 (page 931, right column, lines 18-21). There is no teaching or suggestion in Tannenbaum that co-administration of any combination of IL-12 with IP-10, Mig, or both, would be more beneficial than administration of IL-12 alone.

Discussion of the Lanni Reference

The Examiner's citation of the Lanni reference is mystifying.

Lanni discloses experiments in which the cytotoxic effect of paclitaxel on fibroblasts is investigated. Fibroblasts that express, or do not express, the p53 gene were investigated, and those two groups of fibroblasts were further divided into groups that were, or were not, transformed with the E1A and Ras genes. Lanni hypothesized that paclitaxel might induce release of a cytotoxic cytokine which was responsible for inducing apoptosis of fibroblasts. The fibroblasts were treated with paclitaxel alone or with cephalomannine (a paclitaxel derivative hypothesized not to induce cytokine release) alone.

Lanni observed that medium obtained from macrophages that were induced to apoptose upon paclitaxel treatment could be used to induce apoptosis of fibroblasts. Similar treatment with medium obtained from macrophages that were induced to apoptose upon cephalomannine treatment did not induce fibroblast apoptosis. From these data, Lanni concluded that the cytokine release hypothesis was supported and set out to identify the cytokine. For various reasons, TNF-a was hypothesized to be the cytokine of interest.

Lanni treated macrophages with paclitaxel and collected the macrophage medium following macrophage apoptosis. Fibroblasts were contacted with the medium collected from the apoptosed macrophage culture. Non-treated medium (second bar, from left to right, in Figure 3) rendered about three-quarters of fibroblasts non-viable. However, pre-treatment of the macrophage medium with an anti-TNF-a antibody prior to contacting the treated medium and the fibroblasts significantly reduced the fibroblast viability-reducing effect of the macrophage medium. From these data, Lanni concluded that the apoptosed macrophages released TNF-a into their medium, and that paclitaxel therefore induces apoptosis of macrophages through a mechanism that includes release of TNF-a.

Lanni does not disclose local administration of any agent to a tumor. Lanni does not describe administration of a leukocyte attractant, IFN-g, or a second IR1-promoting agent to a tumor in any animal. Lanni does not disclose co-administration of any two (or more) agents to any tumor in any animal.

Lanni appears to be entirely irrelevant to the claimed invention.

Turning to the Examiner's characterization of the Lanni reference, the Examiner asserts that Lanni "show[s] that it is well known in the art that combination therapy have [*sic*] been used to minimize and/or avoid chemotherapeutic resistance by tumor cells." That assertion appears to be erroneous. Lanni does not disclose or suggest combination of <u>any</u> two or more therapeutic agents (whether administered to tumors or not).

Rejection Pursuant to 35 U.S.C. § 103(a) Over Lee in View of Tannenbaum or Lanni

The Examiner rejects claims 1, 3, 13-17, 19, 20, 25-29, and 31-39 pursuant to 35 USC 103(a) over Lee in view of either Lanni or Tannenbaum. The Applicant respectfully contends that the Examiner has not set forth a *prima facie* case of obviousness, and that this rejection is improper for that reason.

Per MPEP § 2143, in order to establish a *prima facie* case of obviousness, the Examiner must meet three criteria:

> 1) The Examiner must demonstrate that the combined references teach or suggest every element of the claimed methods;
>
> 2) The Examiner must demonstrate suggestion or motivation to combine the teachings of the cited references, and that suggestion/motivation must occur either in the cited references or in the knowledge generally available to one of ordinary skill in the art; AND
>
> 3) The Examiner must demonstrate that if the teachings of the cited references were combined, then one of ordinary skill in the art would have had a reasonable expectation that the combined

teachings could be successfully used to achieve the purposes of the claimed methods.

The Applicant respectfully contends that the Examiner's rejection fails to satisfy any of these three criteria.

Every Claimed Element

All of the rejected claims recite local administration of IFN-g and a leukocyte attractant to a tumor in a human patient.

The Lee, Tannenbaum, and Lanni references are discussed above in detail. None of those three references teaches local administration of IFN-g or a leukocyte attractant to a tumor in any animal.

For that reason alone, the Examiner's rejection fails to meet the criteria of a *prima facie* case of obviousness.

Motivation to Combine References

The Applicant respectfully contends that the Examiner has not properly shown that either the cited references or the knowledge generally available in the art provides sufficient motivation for one of ordinary skill in the art to combine the reference in the manner suggested by the Examiner

The Examiner's purported motivation for combining the cited references is that the Lanni reference is purported to "*show that it is well known in the art that combination therapy have been used to minimize and/or avoid chemotherapeutic resistance by tumor cells. ... Therefore it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to combine known anti-tumor agents to kill tumor cells in a human patient because inducing tumor cell death in a human patient is desirable.* (Office Action, page 4, lines 10-16). The Examiner asserts that the claimed invention does not teach any unexpected results, and that the only difference between the claimed methods and the combined references is an "administration schedule."

The Applicant respectfully contends that the Examiner's comments demonstrate that the Examiner fails to grasp what is claimed. The Applicant is not claiming a mere conglomeration of known methods. As described in the specification (e.g., as summarized in the paragraph bridging pages 7 and 8 of the specification), the claimed method is a synergistic combination of induced tumor antigen release (i.e., effected by local administration of an antigen-releasing agent), leukocyte attraction (i.e., recruitment of leukocytes to the tumor site by local administration of a leukocyte attractants), and induction of an anti-tumor type 1 inflammatory response (i.e., effected by local administration of IFN-g and a second IR1-promoting agent, which induce the attracted leukocytes to mount a type 1 {i.e., cytotoxic} immune response against the tumor cells from which the antigens were released). In contrast, the Examiner has cited non-related methods that can only be related to one another by hindsight reconstruction of the invention that is disclosed for the first time in the Applicant's specification.

The Examiner asserts that the Lanni reference discloses that combinations of known anti-tumor agents can been used to minimize and/or avoid chemotherapeutic resistance by tumor cells. This teaching does not appear anywhere in the Lanni reference (nor does the Examiner cite any portion of the Lanni reference at which this purported teaching occurs). Lanni teaches use of only individual agents (paclitaxel, cephalomannine, or conditioned macrophage medium) to induce apoptosis of macrophages or fibroblasts. Lanni does not teach or disclose <u>any</u> combination of anti-tumor agents. For that reason alone, the Examiner's reliance on the Lanni reference to combine the Lee and Tannenbaum reference is unjustified.

The Lanni reference mentions only a single agent (TNF-a) that is even recited in a pending claim, and does not disclose or suggest combination of that agent with any other agent recited in the claims or disclosed in the Applicant's specification. Furthermore, the Lanni reference does not teach or disclose combining administration of any agent disclosed in the Lanni reference with any agent disclosed in the Lee or Tannenbaum references, nor does it disclose or suggest combining any agent disclosed in

the Lee reference with any agent disclosed in the Tannenbaum reference. Most importantly, however, the Lanni reference contains no direction that would lead an ordinarily-skilled artisan to combine administration of the FOUR AGENTS recited in the Applicant's claims in the manner that is set forth in those claims.

The Examiner has, in effect, simply asserted that multiple treatments are better than one. On that basis alone, the Examiner purports that the teachings of Lee, Lanni, and Tannenbaum can be combined, simply because the references are purported to relate to potential anti-tumor treatments.

No reference or combination of references cited by the Examiner teaches the desirability of combining prior art teachings or suggestions regarding LOCAL ADMINISTRATION TO A TUMOR OF ALL FOUR AGENTS RECITED IN THE CLAIMS. The Lanni reference provides no rationale for combining its teachings with either of Lee or Tannenbaum, nor does it provide any rationale for combining the teachings of Lee with those of Tannenbaum. Because the Examiner has not provided any reason why an ordinarily-skilled artisan would make THE PARTICULAR COMBINATION THAT IS CLAIMED, the Examiner has failed to set forth a *prima facie* case of obviousness for the rejected claims. The Examiner's obviousness-type rejection must be withdrawn for this reason alone.

Reasonable Expectation of Success

In the Office Action, the Examiner provided no information purporting to provide a basis on which an ordinarily-skilled artisan would have a reasonable expectation that the subject matter taught in the cited references could be combined in a way that would achieve the purpose recited in the rejected claims. The combined references do not even include all of the elements of the claim, as discussed above. Furthermore, there is no disclosure in the cited references of the synergy that exists between the steps recited in the claimed methods. For example, release of tumor antigens effected by local administration of the recited antigen-releasing agent is not an end in

itself. Instead, released antigens interact with leukocytes that are attracted to the tumor upon local administration of the recited leukocyte attractant in order to provide a tumor-specific leukocyte response (i.e., the leukocytes attack tumor cells) when those leukocytes are activated upon local administration of the recited IFN-g and second IR1-promoting agent to the tumor.

This synergy is neither taught in any one of the cited references nor in the combined references. Absent an understanding of this synergy (disclosed for the first time in the Applicant's specification), an ordinarily-skilled artisan would have no reason to combine administration of the particular agents recited in the claims, and would also have no reason to believe that the combined administration would have anything other than a merely additive effect (at best). Indeed, the ordinarily-skilled artisan would not be able to tell whether the methods taught in Lee, Tannenbaum, and Lanni are even compatible with one another (i.e., they might not even work if combined). Because the cited references fail to teach the claimed method and provide no expectation that the synergistic effects of the claimed method can be achieved, based only on what is taught in the references themselves, the Examiner has failed to set forth a *prima facie* case of obviousness, and the obviousness-type rejections must be withdrawn.

To summarize, the Examiner provides no proper motivation to combine the cited references. Even if the cited references are combined, they do not disclose every element of what is claimed. An ordinarily-skilled artisan would have no reason to believe that the combined subject matter of the Lee, Tannenbaum, and Lanni references could be used as recited in the claims to induce death of tumor cells in a human patient.

For the foregoing reasons, the Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1, 3, 13-17, 19, 20, 25-29, and 31-39 pursuant to 35 USC 103(a) over Lee in view of either Lanni or Tannenbaum.

Rejection Pursuant to 35 U.S.C. § 103(a) Over Lee in View of Tannenbaum or Lanni and Further in View of Other References

The remainder of the Examiner's 35 U.S.C. § 103(a) rejections (relating to claims 7-12, 17, 18, 30, and 40-66) rely on Lee + (Tannenbaum or Lanni) + (another reference). None of the other reference corrects the deficiencies of the Lee, Tannenbaum, and Lanni references, and the Examiner's rejection of these claims is improper for the same reasons referenced above. The cited references fail to teach every element of the claims, even when all of the cited references are combined (e.g., no reference teaches local administration of IFN-g to a tumor in a human patient). There is no motivation to combine any of these references, and no expectation that an anti-tumor type 1 inflammatory response would be induced even if the cited references were combined. Reconsideration and withdrawal of the Examiner's rejection of claims 7-12, 17, 18, 30, and 40-66 pursuant to 35 U.S.C. § 103(a) are requested for that reason.

Summary

For the reasons set forth above, the Applicant respectfully contends that each of claims 1-66 and 81-83 are in condition for allowance. Reconsideration and withdrawal of the Examiner's rejections and issuance of a Notice of Allowance are requested at the earliest possible time.

Respectfully submitted,

Eugene Roussel

11 August 2003
(Date)

By: _____

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Enclosures: Petition for a One-Month Extension of Time
Euroclone Inc. Description of RPMI 1640 medium composition

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